(d) Objective Considerations of Nonobviousness

Objective indicia of non-obviousness are also critical. It may be "the most probative and cogent evidence in the record" and must be considered. *Fromson v. Advanced Offset Plate,* 755 F.2d 1549, 1556-58 (Fed. Cir. 1985). Genencor fails to address these objective criteria, sometimes called "secondary considerations," and they are fatal to its obviousness claim.

The '031 invention solved a long felt need by others, including Genencor and the failure of earlier products that could not meet customer requirements. **NPF, ¶368**. *Graham*, 383 U.S. at 17-18; *In re Rouffet*, 149 F.3d 135, 1355 (Fed. Cir. 1998). Spezyme Ethyl, embraced by the claims of the '031 patent, is a direct example of the commercial success of the claimed invention. **NPF, ¶369-70**. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988). Sales of the infringing Spezyme Ethyl product have increased dramatically since its introduction, and have taken sales from the only comparable alternative, Novozymes' separately patented Liquozyme SC. ***Id.*** The circumstances show as a whole that the claimed '031 invention is not obvious. **NPF, ¶339-375**.

What Genencor really thinks of the invention covered by the '031 patent is shown by its own patent application, filed eight years after Novozymes filed its '031 patent, and claiming , *inter alia,* the same 179,180 variants as Novozymes. **NPF, ¶372**. Genencor represented to the PTO that these variants are patentable over the same Suzuki and Machius '95 references it says should fatally dominate here. **NPTB, at 33-34**.

2. The Claims Are Enabled By the Specification

Genencor argues that claims 1 and 3 are too broad, because "95% homology" encompasses many variants. **GPTB, at 26-28**. However, the PTO Examiner considered this, and found enablement for as low as "90% homology." In the issued claims, "95% homology" functions with other claim limitations: the 179,180 deletion, and the need for alpha-amylase activity. **NPF, ¶242**. The specification shows how to make and test variants, which is routine and not undue. **NPF, ¶245-48, 382**. Genencor actually agrees: it claimed 90% homology in its own application for the

same variants. **TE-202, A8532.44-45** (claims 1, 3). Even Dr. Klibanov admitted that he could make the 179,180 deletion in a *B. stearothermophilus*. **A6005:18-A6006:5**.

A patent specification need not describe each and every embodiment that falls within the scope of its claims. 35 U.S.C. §112; *Uttler v. Hiraga*, 845 F.2d 993, 998 (Fed. Cir. 1988). A patent "preferably omits from the disclosure any routine technology that is well known at the time of the application." *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1254 (Fed. Cir. 2004).

As the Federal Circuit has said, "[I]t is imperative when attempting to prove lack of enablement to show that one of ordinary skill in the art would be unable to make the claimed invention without undue experimentation." *Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1343, 1360 (Fed. Cir. 1998). Genencor has not, and cannot do that here. The protein engineer would generally make the fewest alterations that do the job (**NPF, ¶28; A5177:5-18**), and had ample guidance in the literature about what to conserve and what might be usefully changed. **NPF, ¶245-48, 382**. Variants can be rapidly and routinely screened. **NPF, ¶245**. A 95% homology threshold provides reasonable protection, so that a few other residue changes will not excuse misappropriation of the invention and its benefits. **NPF, ¶243**. There is no basis to contradict the patent, the Examiner, industry custom, or Genencor's admission, based on an ersatz numbers game. There is no reason to overturn the patent on enablement grounds.

C. Claim Construction

Genencor offers a menu of alternative claim constructions, each of them incorrect. They depart from the ordinary meanings understood by a protein engineer, ignore the patent itself, distort the file history, and break cardinal rules of claim construction. *See Vitronics Corp. v. Conceptronic Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-24 (Fed. Cir. 2005). Limitations cannot be read into a claim from other claims, from the specification, or from patent examples and preferred embodiments. *Unitherm Food Systems, Inc. v. Swift Eckrich, Inc.*, 375 F.3d 1341, 1350-52 (Fed. Cir. 2004); *Sunrace Roots Enter. v. SRAM Corp.*, 336 F.3d 1298, 1305 (Fed. Cir. 2003); *Tandon Corp. v. U.S. Int'l Trade Comm'n*, 831 F.2d 1017, 1023 (Fed.

Cir. 1987). The file history may provide guidance, but can be the least reliable intrinsic source for claim construction. *Phillips,* 415 F.3d at 1317. A proposed special meaning from the file history must be "a clear and unmistakable disavowal" before it can challenge the ordinary meaning and the specification. *Purdue Pharma L.P. v. Endo Pharms., Inc.*, 438 F.3d 1123, 1136 (Fed. Cir. 2006).

1. Parent *Bacillus Stearothermophilus* Alpha-Amylase

Genencor argues that a "parent *Bacillus stearothermophilus* alpha-amylase" in claims 1 and 5 should be taken to mean, "an alpha-amylase having the amino acid sequence of SEQ. ID NO. 3." **GPTB, at 5**. Alternatively, Genencor suggests: "a 514 or 515 amino acid protein encoded by the wild-type *Bacillus stearothermophilus* gene, minus the signal sequence." **GPTB, at 8**. Neither construction arises from customary usage, and neither is one that "stays true to the claim language and most naturally aligns with the patent's description of the invention," *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998).

(a) SEQ. ID NO. 3 Is *Not* the Only Parent or the Only *B. stearothermophilus* Alpha-Amylase

Genencor argues that SEQ. ID NO. 3 is the *only* parent, and the *only B. stearothermophilus* alpha-amylase of the claims. Genencor ignores that claims 1 and 5 provide that SEQ. ID NO. 3 is "for numbering," it is not recited as a source protein which is altered to make the variant, let alone the only one. Genencor ignores the plain meaning of the words, which violates the first canon of claim construction. *Phillips*, 415 F.3d at 1312; *Vitronics,* 90 F.3d at 1582. Genencor ignores that SEQ. ID NO. 3 is one example in the specification, and although it could be a "parent," and is a representative BSG alpha-amylase; it is not the only parent or BSG alpha-amylase. This would violate the cardinal rule that words cannot be read into a claim from the specification. *Unitherm,* 375 F.3d at 1350-52. It would also violate the cardinal rule that a claim is not limited to an example or preferred embodiment. *Sunrace,* 336 F.3d at 1305.

Genencor's defense admittedly would disregard claim differentiation also, by moving SEQ. ID. NO. 3 from claim 3 into the "parent" of claim 1, giving both claims essentially the same scope. **GPTB, at 8**. But claim differentiation is particularly strong where "the limitation in dispute is the

only meaningful difference" between the claims. *Sunrace*, 336 F.3d at 1303; *Kraft Foods, Inc. v. Int'l Trading Co.*, 203 F.3d 1362, 1365-69 (Fed. Cir. 2000); *Tandon*, 831 F.2d at 1023.[10]

There is nothing in the file history so clear and compelling that "parent" must be transcribed as "SEQ. ID NO. 3." Genencor relies on exchanges with the patent Examiner that concerned the variant, and percent homology comparisons for the variant; not the "parent" at all. The '031 application started with a Preliminary Amendment and claims 30-34, comparing a "parent α-amylase" to SEQ. ID. NO. 3 by percent homology. "Parent" had its ordinary meaning, and was supplemented by a different limitation: percent homology. One limitation ("percent homology to SEQ. ID NO. 3") cannot be read into the definition of another term ("parent"). *nCube Corp. v. SeaChange Int'l, Inc.*, 436 F.3d 1317, 1322 (Fed. Cir. 2006). The parent was not defined as "SEQ. ID NO. 3" and could be any suitable parent, which also had "at least 80%, 90%, or 95% homology to SEQ. ID. NO. 3." **TE-101, A7045**. The variants in these claims was not compared to SEQ. ID. NO. 3 for homology; it was used as always "for numbering" the 179,180 deletions. ***Id.***

Another set of claims (35-39), provided "an isolated alpha-amylase enzyme" which further had "at least 80%, 90%, or 95% homology to SEQ. ID. NO. 3," plus the 179,180 deletion. **A7046**. From the start, "parent," "variant," and "alpha-amylase" had their ordinary meanings. From the start, the claims had distinct limitations that further qualified the claimed alpha-amylases according to different percent homology comparisons. In some claims the variant was compared to a parent and in some the variant was compared to SEQ. ID NO. 3. In all of the claims SEQ. ID NO. 3 was used to number the 179,180 deletion. This is just like the claims of the issued '031 patent, e.g. claim 1 (comparison to parent) vs. claim 3 (comparison to SEQ. ID NO. 3). **A7040**.

The Examiner initially rejected claims 30-34 on enablement and written description grounds. **TE-101, A7623-4**. She questioned the scope of the variants: "the currently claimed genus includes variant α-amylases with any number of alterations of the parent enzyme as long as amylase activity

[10] *Sunrace* denounced reading from a dependent claim into an independent claim. Per *Kraft* and *Tandon*, independent claims are also differentiated.

is maintained." **A7624**. Without disturbing the meaning of "parent," she suggested that the variant vs. parent comparison could be supplemented by a percent homology comparison to SEQ. ID NO. 3. **A7627**. Novozymes responded by amending claim 30 to recite, "wherein said variant has at least 80% identity to said parent alpha-amylase." **A7634; A7636-7**. This narrowed the claim 30-34 variants and did not affect the "parent" at all, nor alter the other percent homology of parent vs. SEQ. ID. NO. 3. Since these claims always encompassed a parent that expressly could vary from SEQ. ID NO. 3, there could not have been a redefinition of "parent" to mean just SEQ. ID NO. 3.[11]

The Examiner saw that the amended claims were "directed to a genus of variants of a parent alpha-amylase having at least 80% identity to the parent." **A7719**. This was rejected because, "many functionally unrelated polypeptides are encompassed within the scope of these claims." **A7720**. The Examiner suggested adding, "wherein said variant has alpha-amylase activity." **A7721**. (*See* **A7040**, claims 1 and 3). Also, "upon further reconsideration" the percent homology range was still too broad. **A7725, A7722-24**. Nothing implicated SEQ. ID NO. 3 as the meaning of "parent." The Examiner stated, "applicants did not in fact amend the claim exactly as suggested by the examiner, however it is acknowledged that applicants amendments are similar" (**A7725**). The difference between "parent" and "SEQ. ID NO. 3" was always understood. The Examiner's "suggestion" was just that, and Novozymes' alternative was acceptable -- only the percent homology threshold was still questioned. ***Id.***

Novozymes cancelled the claims in favor of claims 48-52, now '031 claims 1-5. Claim 48 (now claim 1) specified 95% homology between parent and variant, not between parent or variant and SEQ. ID. NO. 3. **A7734**. Claim 50 (now claim 3) did not specify a parent, and did compare the variant to SEQ. ID. NO. 3 for 95% homology. ***Id.*** The amendment also added "*Bacillus stearothermophilus*" to claims 48 and 52 (now claims 1 and 5). The §112 rejections was overcome

[11] Contrary to Genencor, **GPTB at 6-7**, the Examiner's statement that 90% homology to SEQ. ID NO. 3 is enabled does not imply that nothing else was enabled, that no other claim language would work, or that "the variant should [or must] be defined by its percent homology to SEQ. ID NO. 3" (***Id.***). Genencor again points to the variant while trying to redefine parent.

because, "the new claims recite a homology of 95%" for the variant. **A7735-6**. As with the original claims, the variant is compared either to a parent or to SEQ. ID NO. 3. The 95% percent homology for either comparison amended the broader range (as much as 80%) to a higher (i.e., narrower) threshold. This was reviewed by the Examiner, and was accepted. **A7791**. Novozymes did not do anything to limit "parent" or "*Bacillus stearothermophilus* alpha-amylase" to SEQ. ID. NO. 3.[12]

(b) The Parent and *B. Stearothermophilus* Alpha-Amylase Do Not Require 514 or 515 Amino Acids Minus the Signal Sequence

Genencor proposes to redefine what everyone understands a *B. stearothermophilus* alpha-amylase is into a description of something else about it. From extrinsic documents, Genencor advances a supposed 1995 belief about a common but not essential characteristic of then-studied BSG alpha-amylases. **GPTB, at 8-10**. These enzymes are not defined by their length, however, either in the patent or in the literature. In essence, Genencor argues that a BSG alpha-amylase (**GCL, ¶19**) is not really a BSG alpha-amylase, if it fortuitously turns out to be truncated at the C-terminus. ***Id.* at 10; A5226:17-5227:5**. This cannot be correct.

B. stearothermophilus is a species of *Bacillus* bacteria, found in soil, that has a gene for producing alpha-amylase. **A5139:23-5141:5**. An alpha-amylase catalyzes reactions to liquefy starch. **A1003**. A "*B. stearothermophilus* alpha-amylase" is an enzyme having alpha-amylase activity that is produced by a *B. stearothermophilus* alpha-amylase gene. **A5138:19-5140:14**. Genencor does not dispute these ordinary meanings, and they control. **A1003; GCL, ¶9-11, 19-20; NPTB, § II.A**. Further, the sequence of an enzyme can be determined, whatever the date, and whatever its actual length. **A5058:5-16; A5163:3-16**. There is no need for a fixed BSG alpha-amylase length as of the '031 filing date, nor that it account for a signal sequence but no other post-

[12] If anything, the "parent" was broadened. Instead of comparing a parent to SEQ. ID NO. 3 for 80-95% homology (original claims 3-33), the parent in claims 1 and 5 is a "*B. stearothermophilus* alpha-amylase." This supports an ordinary meaning. "A broadening claim amendment made during the prosecution history . . . supports a plain-meaning construction of claim 1." *3M Innovative Prop. Co. v. Avery Dennison Corp.*, 350 F.3d 1365, 1372 (Fed. Cir. 2003).

translational modification. **TE-100, at A7040; NPF, ¶20-24, 86-89, 138-40**. There is no need to use a sequence predicted from DNA, rather than the actual sequence, determined empirically. ***Id.***

Genencor's first error is that the meaning of a term does not incorporate unarticulated characteristics that may be believed about the "thing" being named. *N. Telecom Ltd. v. Samsung Elecs. Co.*, 215 F.3d 1281, 1290 (Fed. Cir. 2000) (cautioning against "extraneous" limitations). Second, there is no reason to pick amino acid length as a prized detail, except that Genencor wants to avoid infringement. Third, Genencor would add "514-515 amino acids" to the claim in the guise of a definition, when those words do not appear in the patent and could not be read in anyway. *Id.* Fourth, Genencor would limit the claims to an implicit 514-515 length, based on its own tangential inferences from embodiments in the examples -- but the examples are not limiting. *Phillips,* 415 F.3d at 1323. Fifth, Genencor overlooks that the specification contemplates other exemplary BSG parents, which have varying degrees of homology or cross-reactivity to representative sequences. **A7011, at 41-62**. There is no limit on amino acid length. Other embodiments are contemplated and can include BSG alpha-amylases not yet characterized. *Sri Int'l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1121 (Fed. Cir. 1985) (applicant need not know or describe future embodiments). Sixth, Genencor relies on extrinsic testimony by Dr. Alber and his review of selected literature. **GPTB, at 9-10**. This cannot alter the plain meaning of the claim terms, nor trump the intrinsic record, particularly the claims and the '031 specification themselves. *Phillips*, 415 F.3d at 1319.

Dr. Alber made generalizations from selected pre-1995 literature. **A5208-09**. He spoke only about an expected length for a BSG alpha-amylase, "if they had gone to the trouble of sequencing one in 1995." **A5209:11-17**. He spoke from his reading of "literature on alpha-amylase gene sequences and on the corresponding protein sequences that were reported." **A5209: 18-24**. DNA was used to predict amino acid sequences that were not actually determined. **A5507: 14-16**. At most, imprecise molecular weight gels were run (**A5505:22-25; A5507:25-3**), and only the N-terminus was sequenced. **A5210:8-18** (Ihara paper). N-terminus truncation was observed (the signal sequence), but the rest of the protein (including the C-terminus) was not sequenced. ***Id.*** As

Dr. Alber admitted, "The only way to tell exactly how many amino acids are in a protein is to sequence it or use mass spec" (**A5510:8-11**). And even if he saw nothing "inconsistent" with an educated guess at 514-515 amino acids (**A5215-16**) (gene bank listings); there was nothing from which to require or define a BSG alpha-amylase that way.[13]

Ultimately, Genencor relies on a false syllogism: *As of 1995, BSG alpha-amylase genes were generally described as encoding a 514-515 amino acid protein. Enzyme "X" does not have 514-515 amino acids. Therefore, enzyme "X" is not a BSG alpha-amylase.* Even assuming the initial premise is correct, there is no connection between amino acid length and how the protein engineer identifies and names an enzyme -- according to its origin and function. **A5138:19-5140:14; A1003**. An example illustrates the point: *The apples we have seen to date are red. This fruit is green. Therefore, this fruit is not an apple.* Obviously, an apple is not defined by its color, nor by when green apples first became known. The same is true for amino acid length; it does not define a *B. stearothermophilus* alpha-amylase.

(c) G997 Is A "*B. stearothermophilus* Alpha-Amylase"

Genencor argues that G997 cannot be a "*B. stearothermophilus* alpha-amylase" of the '031 claims, because it is truncated and does not have 514-515 amino acids. **GPTB, at 10-11**. This is wrong for the reasons given above. It is also wrong because comparing an industrially produced variant BSG alpha-amylase (Spezyme Ethyl) to its industrially-produced *BSG* alpha-amylase precursor or parent (G997) is the right thing to do. **NPF, ¶323-30**. Both alpha-amylases are made by expressing the alpha-amylase gene of a BSG organism under conditions to obtain industrial quantities. **GPF, ¶52-59; GCL, ¶19; NPF, ¶124-25**. This is a one-to-one comparison, using samples from Genencor. **NPF, ¶129-37**. Directly comparing them is what claims 1 and 5 of the

[13] The possibility of C-terminal truncation was known. **NPF, ¶20-24**. As Dr. Arnold testified, "We didn't know [specifically about truncated BSG] in 1995, because we never asked that question." **A5181:19-20.** When the actual sequence was determined, the inherent truncation was seen. **A5181:20-23**. Other tests also show truncation of wild-type BSG alpha-amylase. **NPF, ¶129-149**. Dr. Alber pointed to articles where artificial C-terminal truncations were made, and many were active, with less than 514-515 residues. **A5217:9-A5220:2**; **A5255:21-25**.

patent say to do. **TE-100, A7040**. It is what a protein engineer would do, and what Genencor's Judy Chang did do. "Commercially available G997" was "used for this comparison" with EBS2 (a/k/a Spezyme Ethyl). **TE-161, A8366**. Genencor's work, and experiments by Dr. Jorgensen from Novozymes, show that G997 and Spezyme Ethyl have the same post-translational truncation at the C-terminus, and differ only by the 179,180 deletion. **NPF, ¶129-149**. Dr. Chang found that they all had "less than the theoretical molecular weight -- even for the wild-type G997 produced in stearothermophilus, indicating that the secreted, mature protein is truncated." **TE-161, A8368**.

The use of an industrial process does not mean that G997 is not a wild-type alpha-amylase, as Genencor's own documents and witnesses show. **TE-161, A8365, 8368; A5040:1-2; A5045:16-19**. G997 is was expressed from an unaltered wild-type gene, as Genencor admits. ***Id;*** **NPF, ¶124-25, 142**. The G997 DNA has not been manipulated to produce an altered protein sequence, i.e. to make a variant. G997 is a wild-type enzyme expressed from wild-type DNA, and is the BSG alpha-amylase for comparison with its variant, Spezyme Ethyl. Both enzymes have post-translational truncations, which in no way affects the meaning of any claim terms in the Novozymes patent.

Genencor seeks to use the specter of industrial conditions to create a false doubt. **GPTB, at 10-11**. In fact, all of the evidence converges on one consistent sequence for G997. Dr. Jorgensen found one and only one sequence for G997, in different Genencor samples tested at different times. **TE-123, A8343; TE-199, A8529; TE-226, A8556.1; NPF, ¶129-37**. Genencor got the same result, a 29 amino acid truncation from the predicted sequence. **TE-161, A8369; NPF, ¶141-49**.

Genencor's Judy Chang found "no fragments within 27-29 residues of the C-terminus," which was consistent with the molecular weights she measured. **A8368-9**. This was not a mixture. Within the precision of the digest mapping and molecular weight methods she used, the truncation for both EBS2 (Spezyme Ethyl) and G997 was only resolved to within 27-29 residues. **A8365, n.1; A8368-69, Fig. 3; NPF, ¶141-49**. Still, the only difference was the double-deletion. **NPF, ¶145**. Dr. Alber's cavalier interpretation of "27-29" was that Chang's G997 was "not a pure sample" (**A6011:6-21**) and had three truncations. ***Id.*** This might say something about Chang's work, but

does not mystify G997 itself. No purity criticism has been made of the Jorgensen G997 samples, which uniformly showed only one 29 residue truncation. **NPF, ¶129-37**. The same is true for the undisputed Spezyme Ethyl sequence. **NPF, ¶128**. Apart from the Chang report, Genencor has no experiment or data and made no effort to pin down the G997 sequence or test the variability idea. Novozymes did do the experiment, and no variability was found. In sum, additional work confirmed that the 29 residue truncation is the correct one. **NPF, ¶129-37**. There is no homogeneity problem, nor is the G997 sequence variable and uncertain. There is no "moving target," except that Genencor would have it so to avoid infringement.

It is not a problem even if G997 came in three versions. Slight variability arising from Chang's test methods, or hypothetically from expression of the protein itself, cannot "disqualify" G997 as a *B. stearothermophilus* alpha-amylase or parent of the claims. A comparison with Spezyme Ethyl can still be made, using the preponderant consensus sequence. **NPTB, at 22-26**.

A comparison with all three sequences would not change the outcome. According to the Chang report, Spezyme Ethyl has the same variability as G997. **A8368-69**. So, each truncation in G997 has a corresponding Chang truncation in Spezyme Ethyl. For an apples-to-apples comparison, the only difference is still the double-deletion, just as in claim 5. **NPF, ¶154-58, ¶334-35**. For claim 1, the percent homology comparison would be between each possible G997 truncation and its matching Spezyme Ethyl truncation. According to GAP and the patent, this would always be 100% homologous (**NPTB, at 22-25**), because each sequence is the same, except for the double-deletions, which is not counted. ***Id***. Even if the deletions and truncations are counted, the largest difference between G997 and Spezyme Ethyl would be four residues: the double-deletion plus two residues at the tail (29-27=2). So G997 would have 488 amino acids, four more than the undisputed 484 amino acid sequence of Spezyme Ethyl. This works out to 484/488 = 99.2% homology -- using Genencor's "count everything" approach. **GPTB, at 16**. This is still within "at least 95%" as claimed. Claim 3 compares Spezyme Ethyl to SEQ. ID NO. 3 and is not affected by G997.

There is no problem with G997; it is unmistakably a "*B. stearothermophilus* alpha-amylase" and qualifies as a "parent" of the '031 claims.

2. Percent Homology Means Percent Identity According to GAP; *Not* Counting Unmatched Residues

The claimed variants are "at least 95% homologous" to either a parent (claim 1) or SEQ. ID. NO. 3 (claim 3). Percent homology in the patent means "percent identity," and is calculated according to a standard method, as implemented by the GAP (GCG) program. **NPTB, at 18-20**.

The GAP method uses a "count what matches" approach. The number of exactly matching amino acid residues in two sequences is compared to the total number of residue positions that appear in both sequences, expressed as a percent. **NPF, ¶97**. GAP and other known programs use this method, and any of them may "suitably be used." **NPF, ¶99**. Other lesser known programs employed a "count everything" method. **GPF, ¶216-20**. The patent does not direct the use of these other methods, nor point to other programs which do not use the standard GAP method. **NPF, ¶99; TE-100, at A7001-7040**. Using GAP or an equivalent program is straightforward. The percent identity is automatically calculated from the alignment and is displayed in a report. **A5114:14-17; TE-126, A8347**. There is no mystery about how percent identity is "revealed," as Genencor would have it. **GPTB, at 12**. The patent is clear and unambiguous, a "sequence is to be considered X% homologous" when the alignment "reveals an identity of X%," according to "the GAP computer program" which may "suitably be used," i.e. with others than work the same way. **TE-100, A7009 at 4:36-45; NPF, ¶90-101**. The protein engineer would follow the directions in the patent; he or she would not go do something else. **A5129:19-24**; **A5141:21-5142:3**.[14]

Other statements in the patent do not lead elsewhere. The disputed term is "percent homology." Genencor focuses on a *different* claim term ("variant") in order to confuse the issue. A discussion of variant "deletions" can not be read into "percent homology" from the specification.

[14] Genencor makes much of "may suitably be used." Quite simply, a program that calculates percent homology differently is not identified as "suitable." That other programs and methods were known does not make them suitable, and does not mean that any of them *must* be used, *instead* of the method and representative GAP implementation that is in the patent.

Unitherm, 375 F.3d at 1351. The deletions cannot be read into "percent homology" from another limitation. *Phillips*, 415 F.3d at 1325. A definition in the specification is not altered or discounted by a bait-and-switch to other disclosures. *Vitronics,* 90 F.3d at 1582. The specification's definition also cannot be overruled by extrinsic evidence, such as testimony by Genencor's Dr. Alber. *Id.*

For example, Genencor quotes from the patent that (**GPTB, at 13**)(emphasis added) (citing **TE-100, A7009 at 3:59-65**), "the variants" of the invention include those in which "at least one amino acid residue of the parent alpha-amylase has been deleted." A variant is made by altering the amino acid sequence of a source or parent, by addition, deletion or substitution. **TE-100, A7009 at 3:59-65**. This is about the "variant," not "percent homology." ***Id***. The claimed variants have a 179,180 deletion relative to SEQ. ID NO. 3. **A7040**. The alpha-amylase gene is modified so that these residues are left out when the gene is expressed. **NPF, ¶18-27**. This is a different claim limitation and does not address how much the variant otherwise differs from its parent or SEQ. ID NO. 3 by "percent homology." This is a different question, and is answered, not by manipulating residues, but by comparing sequences according to a standard percent homology (identity) method, embodied in a well-known program, according to a clear disclosure in the patent. **NPF, ¶90-101**.

Dr. Arnold did not depart from this view in an earlier litigation. In her Declaration regarding the related '038 patent, she stated (**A8879-80, ¶13**) (emphasis added):

> In addition to identifying specific differences, (e.g. additions, substitutions or deletions) between two sequences, the overall sequence identity of two sequences (e.g. parent and variant) can be compared. The '038 patent uses the term "homology" to mean sequence identity … Sequence identity is a measure of the total degree of sequence identity, often expressed as a percent. … According to the '038 patent, "an amino acid sequence is considered to be X% homologous to the parent alpha-amylase if a comparison … reveals an identity of X%" [citation omitted] In particular, "the GAP computer program … may suitably be used" ….

The percent homology comparison is "in addition to" (not part of) sequence differences that produce a variant. "In particular" the patent points to the GAP program; it is the particular method of comparison used. ***Id.*** There is nothing to indicate or require other programs or methods. **A8882, ¶19**. Although GAP is "one way," i.e. one program, Dr. Arnold made clear that, "The percent

homology between these two sequences is the percent identity reported by the GAP program." **A8883, ¶21**; **A8885, ¶26, 28, 29**. Genencor relies on **A8886, ¶30**, but what Dr. Arnold actually said was that she was "not counting the gap at 180-181 of SEQ. ID NO. 3" and that "This gives an aligned sequence identity of 99.414 percent according to the GAP algorithm." ***Id.*** (emphasis added). A further gap-neutral and "by-hand" calculation was noted (***Id.***), which does not change the patent.

There is no express or implied direction in the '031 specification to count all deletions, which would contradict and supersede the express guidance in the patent and the industry standard at the time: a "count what matches" method used by GAP. **TE-100, A7009, 4:36-49**. Genencor argues for an extrinsic calculation, one not found in the patent. Genencor pleads that other programs "such as the ALIGN and GAP(Huang) programs" must be used, or a "by hand" count must be done, so that alignment gaps are included. **GPTB, at 16**. This cannot be correct. Extraneous options cannot control, and a claim construction that does not encompass a disclosed embodiment is "rarely, if ever, correct." *Vitronics*, 90 F.3d at 1583. Knowing that it infringes pursuant to the GAP calculation, Genencor argues for an interpretation of % homology that excludes the only disclosed method in the patent. **GPF, ¶209-221**. The inventors had every right to do it their way, *Marley Mouldings, Ltd. v. Mikron Indus.*, 417 F.3d 1356, 1361 (Fed. Cir. 2005), and Genencor's wish cannot change the patent. *Johns Hopkins*, 152 F.3d at 1355.

Genencor took a contrary position in its own U.S. patent application for BSG alpha-amylase variants (including SPEZYME Ethyl). These variants have the same 179,180 deletions as the '031 claims. **TE-194, A8521; NPF, ¶237**. According to Genencor (**TE-202, A8532.17 at ¶[0056]**):

> A polynucleotide or a polypeptide having a certain percent (e.g. 80%, 85%, 90%, 95%, or 99%) of sequence identity with another sequence means that, when aligned, that percentage of bases or amino acid residues are the same in comparing the two sequences. This alignment and the percent homology or identity can be determined using any suitable software program known in the art.

Genencor suggests a number of programs and GAP is prominent among them. **TE-202, A8532.17 at ¶[0096]**. Genencor did not require protein engineers to count gaps or to use only gap-counting

programs, as it now argues. And where Genencor specified several programs, the '031 patent was more particular: only GAP is named; only its method is implicated.

D. Genencor and Spezyme Ethyl Infringe Claims 1, 3 and 5

When the claims are properly construed, Spezyme Ethyl infringes claims 1, 3 and 5 of the '031 patent. **NPTB, at 22-26**. Genencor offers misplaced readings of "parent," "*B. stearothermophilus* alpha-amylase" and "percent homology" to escape its actions. **GPTB, at 5-20**.

Genencor admits that claim 1 is infringed, unless Spezyme Ethyl is compared to SEQ. ID NO. 3 instead of its actual G997 parent, and if the percent homology comparison is done according to a method that counts all gaps, i.e. emphatically not using the GAP program. **GPTB, at 17**. Novozymes has shown, and it is not disputed, that Spezyme Ethyl is 98.967% identical to SEQ. ID NO. 3 according to GAP, which is "at least 95%." So, even if claim 1 is rewritten to make the "parent" into the SEQ. ID NO. 3 of claim 3, there is still infringement according to GAP. **NPF, ¶162-65, 331-34**. Furthermore, if the proper comparison to the G997 parent is made, the result is "at least 95%" homology, even using Genencor's "simple arithmetic" to count all the gaps. **GPTB, at 16-17**. Under any percent homology scenario, including Genencor's erroneous proposal, the result is more than 95%, and claim 1 is still infringed. Genencor's confusing alternative definitions for "parent" and/or "*B. stearothermophilus* alpha-amylase" do not change this analysis.

Claim 3 compares Spezyme Ethyl to SEQ. ID NO. 3, so arguments about "parent *B. stearothermophilus* alpha-amylase" do not apply. When GAP is used for homology, the result is 98.967%. Genencor's infringement is plain. **NPTB, at 18-20**.

Claim 5 is also infringed. Genencor's documents show, Novozymes' experiments confirm, and the record amply proves, that the only difference between Spezyme Ethyl and the G997 alpha-amylase it came from is the 179,180 deletion. **NPF, ¶136, 141, 334-35; GCL, ¶19**. "Homology" is no help to Genencor here, because it is not part of the claim. "Parent" is not in the claim either. Genencor can only argue that a BSG alpha-amylase is not a BSG alpha-amylase (a rose is not a

rose). By swapping SEQ. ID NO. 3 for BSG alpha-amylase, Genencor creates a false comparison to avoid the claim. For all of the reasons given previously, this argument must fail. **NPF, ¶80-84.**

Genencor's argument that infringement can somehow be avoided depending on when or how the product was made is baseless. **GPF, ¶¶54-56.** The amino acid sequence for Spezyme Ethyl is admitted and has not changed. **GPF, ¶52.** However it is now manufactured, it is the same enzyme, derived from the same G997 source, and infringes for all of the same reasons.

Genencor also argues that the actual G997 sequence should be ignored, in favor of a hypothetical 514-515 residue comparator, or a theoretical but *disproved* 515 reside G997 coding sequence. **GPTB, at 18-19; TE-161; ¶20-24, 86-89, 138-40.** This would artificially introduce more than the two deletions of claim 5. Genencor would mix and match to suit its purposes, and would compare a phantom alpha-amylase to Spezyme Ethyl instead of its actual source, as claim 5 requires. This is blatantly wrong, for all of the reasons given above. **NPF, ¶20-24, 86-89, 138-40.**

Without trying to find out, Genencor pretends that G997 may have more than one sequence and so is "uncertain." **GPTB, at 19-20.** As shown above, all the work actually agrees on one G997 sequence. **NPF, ¶129-37.** The supposed variation comes from the Chang report (**GPTB, at 10-11; TE-161**), which left open whether G997 and Spezyme Ethyl had a 27, 28 or 29 residue truncation. ***Id.*** This was settled by Novozymes' repeated experiments showing only one sequence. **NPF, ¶129-149.** Genencor admits that Spezyme Ethyl has only one sequence. **GPF, ¶52; NPF, ¶128.** They both have the same truncation and differ by the double-deletion. **NPF, ¶129-49, 160.**[15]

In sum, claims 1, 3 and 5 of the '031 patent are infringed by Genencor's Spezyme Ethyl.

IV. CONCLUSION

For all of the reasons given, the Court should enter judgment that the '031 patent is valid, enforceable and infringed. **NPTB, at 40.**

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[15] Spezyme Ethyl has 484 residues. **NPF, ¶128; GPF, ¶52.** G997 has 486 residues. The only difference is the 179,180 deletion. **NPF, ¶134, 136.** According to Genencor's calculation, this is a homology of 484/486 = 99.6%. Even if G997 has as many as two more residues, according to the dubious truncation theory, this is 484/488 = 99.2%. **NPF, ¶141-49; GPF, ¶168-185.**

Respectfully submitted,

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CERTIFICATE OF SERVICE

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